

Laser Microsurgery Versus Radiotherapy Versus Open Partial Laryngectomy for T2 Laryngeal Carcinoma: A Systematic Review of Oncological Outcomes

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Flaminia Campo, MD¹, Jacopo Zocchi, MD², Massimo Ralli, MD, PhD¹ ,
Daniele De Seta, MD, PhD³, Francesca Yoshie Russo, MD, PhD¹ ,
Diletta Angeletti, MD¹, Antonio Minni, MD¹, Antonio Greco, MD¹,
Raul Pellini, MD², and Marco de Vincentiis, MD⁴

Abstract

Introduction: The aim of the current systematic review is to update the pooled survival outcome of patients with T2 glottic carcinoma treated with either laser surgery (CO₂ transoral laser microsurgery [CO₂ TOLMS]), radiotherapy (RT), or open partial laryngectomy (OPL). **Methods:** A systematic search was performed using the MEDLINE database, Scopus, and Google scholar. The inclusion criteria were studies of patients with T2N0 glottic tumor, treated with either primary CO₂ TOLMS, definitive curative RT, or primary OPL, and with reported oncological outcome at 5 years calculated with a Kaplan-Meier or Cox regression method. **Results:** The results of the current review show that local control (LC) is higher with OPL 94.4%, while there are no differences in LC at 5-year posttreatment for patients treated with RT, compared to those treated with CO₂ TOLMS (respectively, 75.6% and 75.4%). Primary treatment with OPL and CO₂ TOLMS results in higher laryngeal preservation than primary treatment with RT (respectively 95.8%, 86.9%, and 82.4%). **Conclusion:** First-line treatment with OPL and CO₂ TOLMS should be encouraged in selected T2 patients, because it results in higher laryngeal preservation and similar LC compared to primary treatment with RT. The involvement of the anterior commissure in the craniocaudal plane and T2b impaired vocal cord mobility have a poorer prognosis and LC compared to patients with T2a tumors for both CO₂ TOLMS and RT.

Keywords

laser, radiotherapy, open partial laryngectomy, T2 glottic cancer, anterior commissure, oncological outcomes

Introduction

Early glottic cancer (Tis-T2) is a highly treatable disease with excellent survival rates. Many studies examined treatment outcomes for “early stage” laryngeal cancer, grouping those treated for carcinoma in situ (Tis), T1a, T1b, and T2 tumors, but most of the data for early laryngeal cancer are dominated by T1 and Tis cases.^{1,2} However, T1 and T2 glottic cancer are heterogeneous with different growth rates and tendency to infiltrate, and the therapy achieves different results in terms of both oncological and functional outcomes.

Available treatment options include CO₂ transoral laser microsurgery (CO₂ TOLMS), open partial laryngectomy (OPL), or radiotherapy (RT). To date, there is no clear evidence regarding the effectiveness of surgical treatment (CO₂ TOLMS and OPL) over RT, including a recent Cochrane analysis.^{1–6}

The aim of the current systematic review is to compare single-modality treatments for patients with T2 glottic

¹ Department of Sense Organs, Sapienza University of Rome, Rome, Italy

² Department of Otolaryngology and Head & Neck Surgery, IRCCS “Regina Elena” National Cancer Institute, Rome, Italy

³ Unit of Otorhinolaryngology, Department of Surgery, Azienda Ospedaliero-Universitaria Di Cagliari, University of Cagliari, Cagliari, Italy

⁴ Department of Oral and Maxillofacial Sciences, Sapienza University of Rome, Rome, Italy

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Corresponding Author:

Massimo Ralli, Department of Sense Organs, Sapienza University of Rome, Viale del Policlinico 155, Rome 00186, Italy.

Email: massimo.ralli@uniroma1.it



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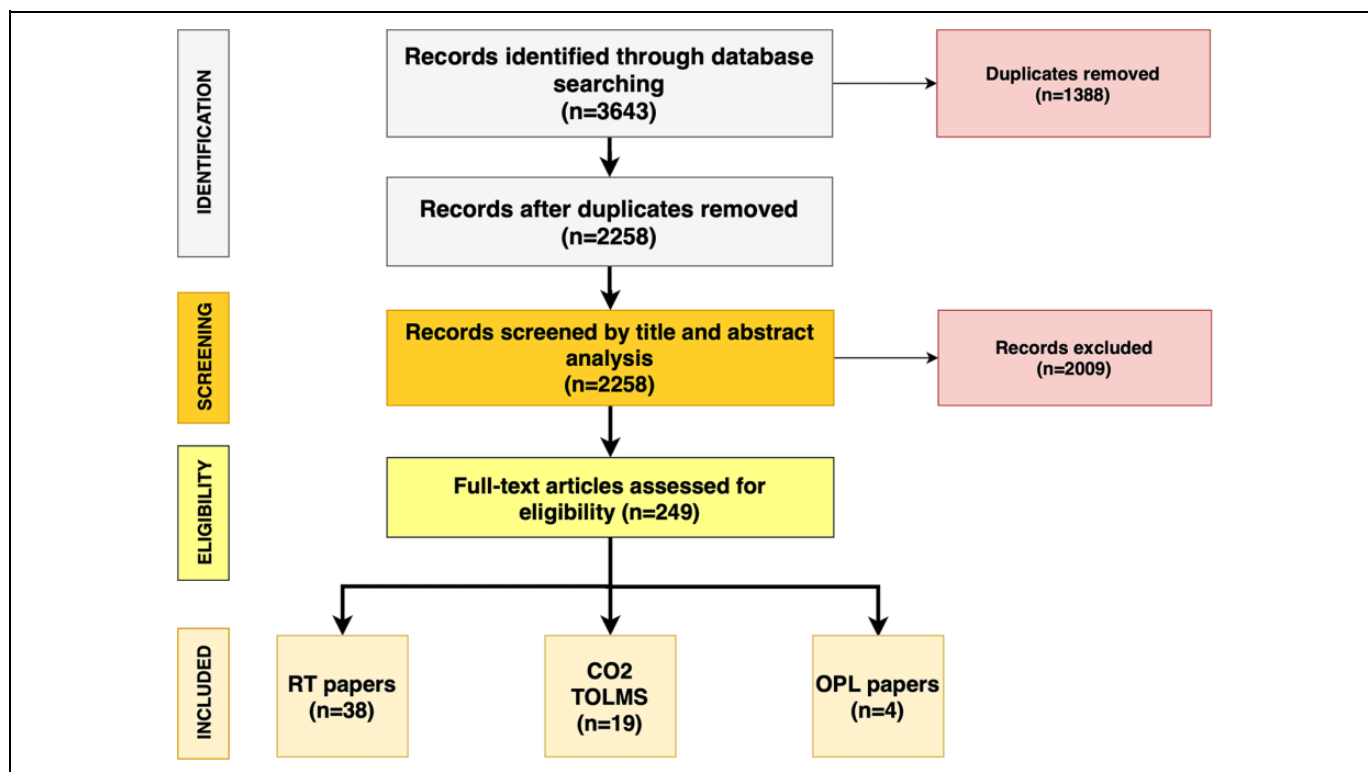


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram followed in this review. The diagram shows the information flow through the different phases of the review and illustrates the number of records that were identified and included.

carcinoma through the analysis of survival outcomes, local control (LC), and laryngeal preservation (LP) in patients treated with either CO₂ TOLMS, RT, or OPL.

Materials and Methods

Search Strategy

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, 2 independent researchers conducted a literature search on articles published as of August 2019 using 3 different databases (PubMed, Scopus, and Google Scholar) with combinations of the following terms: laryngeal cancer, early glottic carcinoma/tumor, laryngeal squamous cell carcinoma, CO₂ TOLMS, RT, and OPL on articles published between January 1990 and August 2019.

Eligibility and Inclusion Criteria

The inclusion criteria were clinical studies in patients with glottic squamous cell carcinoma staged as a T2N0 according to the Union for International Cancer Control's (UICC) TNM Classification of Malignant Tumours—8th edition⁷ treated with either primary CO₂ TOLMS, curative RT, or primary OPL, and with reported oncological outcomes at 5 years calculated with a Kaplan-Meier or Cox regression method. Exclusion criteria were articles not written in English, studies with less than 10 patients, with concurrent chemoradiotherapy, those

describing surgery combined with adjuvant therapy, and those describing surgery or RT as salvage therapy.

Data Extraction

Title and abstract of selected papers were carefully read according to the inclusion and exclusion criteria, and duplicates were removed. The full text of the included studies was reviewed with extraction of following data: (1) patient number, (2) average follow-up time (months), (3) treatment, and (4) 5-year oncological outcome in terms of LC and LP.

Study Quality

The levels of evidence of the included articles were scored according to the standards by Wasserman et al⁸ as follows: level I: randomized controlled trials, level II: prospective study with internal control group, level III: retrospective study with internal control group, level IV: case series without an internal control group, and level V: consensus or expert opinion without critical appraisal.

Results

Search Results

The results of the search are summarized in Figure 1. The initial search identified 3464 studies on MEDLINE database, Scopus, and Google scholar. Articles published after the 1990s were selected and imported into a reference management

Table 1. Oncological Outcomes of Patient Treated With Radiotherapy.

Author (year)	Treatment period	Patients	Gray	Follow-up (months)	LC (%) 5 years	LP 5 years
Tureson (1991) ⁹	1963-1983	132	46-83	Minimum 48	68.9	
Fein (1993) ¹⁰	1977-1989	115	63-76	Minimum 24	84	84.3%
Stevens (1994) ¹¹	1979-1989	31	62	Median 49	70	
Klinterberg (1996) ¹²	1969-1991	94	60-72		73	
Burke (1997) ¹³	1983-1993	27	50-74	Median 63	70.6	
Le (1997) ¹⁴	1956-1995	83	52-76	Median 116	70	
Franchin (1998) ¹⁵	1985-1996	46	63-68	Median 72	70	
Sakata (2000) ¹⁶	1984-1996	50	64 vs 55-58 (CFX vs AF)	Median 69	70.8	
Smee (2000) ¹⁷	1967-1994	116	50-70	Mean 146	72	
Haugen (2002) ¹⁸	1990-1998	45	61-65	Mean 40	88	
Garden (2003) ¹⁹	1970-1998	230	70	Median 82	72	
Stoeckli (2003) ²⁰	2008-2012	30	68-70.2	Mean 70	67	77
Chen (2003) ²¹	1983-2001	46	63-73	Minimum 12	60	63
Zouhair (2004) ²²	1983-2000	36	60-74	Median 85	77	
Frata (2005) ²³	1970-1999	256	61-65	Mean 90	73	
Murakami (2005) ²⁴	1989-1998	27	64-70	Mean 75	61	92
Short (2006) ²⁵	1986-1998	43	60-66 vs 55 (CFX vs HFX)	Median 59	80.5	
Tateya (2006) ²⁶	1987-1998	48	60-72 (CFX vs HFX)	Mean 80		95.2
Dagan (2007) ²⁷	1983-2002	80	63-77	Median 115	82	82
Chera (2010) ²⁸	1964-2006	260	74	Median 144	76.5	
Jones (2010) ²⁹	1987-2006	41	74	Median 70	97.6	
Smee (2010) ¹⁷	1967-2006	142	50-70	Median 91	71.8	
Khan (2012) ³⁰	1986-2006	54	44-69	Mean 67	75.9	
Tong (2012) ³¹	1983-2005	262	57-70	Median 126	79	
Al-Mamgani (2013) ³²	1985-2011	331	66-70	Median 90	78	
Douglas (2013) ³³	1999-2003	128	50-55	Median 71	82	
Karasawa (2013) ³⁴	2002-2010	24	63	Median 47	67.3	
Hoebbers (2013) ³⁵	2000-2011	120	60	Median 38	78	
Higashino (2014) ³⁶	2004-2011	20	70	Mean 60	80	
Moon (2014) ³⁷	2002-2010	16	70 vs 68 (CFX vs HFX)	Median 67	56.3-77.8	
Rutowski (2014) ³⁸	2002-2009	115	45-70 IMRT	Minimum 36	72	
Motegi (2015) ³⁹	1999-2007	44	65 (AF)	Minimum 24	77	95
Ermis (2015) ⁴⁰	2004-2013	64	55 (HFX)	Median 72	80.9	
Lim (2015) ⁴¹	1981-2010	67	67	Median 85	72	
Harada (2015) ⁴²	1991-2010	35	74.4	Median 61	86	97
Portenza (2015) ⁴³	2000-2010	16	66	Median 75	84	
Zumsteg (2015) ⁴⁴	1981-2011	70	60 (CFX vs IMRT)	Median 59	75.8	
Sert (2019) ⁴⁵	2005-2015	21	65.25 Gy in 29 fractions	Median 64	56	

Abbreviations: AF, accelerated fractionation; CFX, conventional fractionation; DSS, disease-specific survival; Gy, gray; HFX, hypofractionation; IMRT, Intensity-modulated radiation therapy; LC, local control; LP, larynx preservation; OS, overall survival.

software (Endnote, Clarivate Analytics). After the removal of duplicates, 2258 publications were identified. Papers were screened in title and abstract, and 249 manuscripts were reviewed in full text. Sixty-one studies met the inclusion criteria; of these, 38 RT papers, 19 CO₂ TOLMS studies, and 4 OPL article provided 5-year oncological outcome data for 1452 patients treated with CO₂ TOLMS, 3365 patients treated with RT, and 366 patients treated with OPL.

Study Characteristics

All 61 included studies were published in peer-reviewed journals and were case series without an internal control group, a level IV evidence. No randomized controlled trials studies were identified.

Oncological Outcomes

Tables 1, 2, 3, and 4 show the oncological results of patients treated with either CO₂ TOLMS, RT, or OPL in the studies included in this systematic review. The results of the analysis show that weighted averages of LC was higher with OPL (94.4%), while there were no differences in LC at 5 years for patients treated with RT, compared to those treated with CO₂ TOLMS (respectively, 75.6% and 75.4%). Primary treatment with OPL and CO₂ TOLMS resulted in higher LP in the long term compared to primary treatment with RT (respectively, 95.8%, 86.9%, and 82.4%).

Discussion

The main treatment modalities for early glottic carcinomas include CO₂ TOLMS, RT, and OPL; however, there is no clear

Table 2. Oncological Outcomes of Patient Treated With CO₂ Transoral Laser Microsurgery.

Author (year)	Treatment period	Patients	Follow-up (months)	LC 5 Years (%)	LP 5 years (%)
Eckel (2000) ⁴⁶	1987-1996	93	Mean 55	82	93.1
Peretti (2000) ⁴⁷	1987-1994	23	Mean 76	91	
Motta (2005) ⁴⁸	1991-1998	236	Mean 60	66	82.5
Peretti (2005) ⁴⁹	1998-2001	55	Mean 58	77	84.8
Rodel (2009) ⁵⁰	1986-2004	102	Median 65	76	
Mantsopoulos (2010) ⁵¹	1977-2004	143	Mean 139	89.4	
Peretti (2010) ⁵²	1988-2005	109	Mean 84	85.6	95.1
Blanch (2011) ⁵³	1998-2008	81	Mean 45.4	40.7	73.2
Lucioni (2011) ⁵⁴	2000-2007	14	Mean 47.9	78.6	100
Canis (2013) ⁵⁵	1979-2006	269	Mean 96	75.8	88.3
Fang (2013) ⁵⁶	2004-2011	30	Median 33	83.3	
Lee (2013) ⁵⁷	1997-2011	11	Mean 70	81.8	90
Peretti (2013) ⁵⁸	2005-2010	59	Minimum 18		84
Hoffman (2015) ⁵⁹	2001-2013	19	Mean 44	63.6	90.9
Ansarin (2017) ⁶⁰	1999-2013	90	Median 72		91.1
Day (2017) ⁶¹	1995-2011	17	Median 44.6	86	88
Chang (2017) ⁶²	2003-2009	20	Medium 35	84	
Carta (2018) ⁶³	1993-2005, 2010-2016	41	Median 52	79.5	88
Pedregal-Mallo (2018) ⁶⁴	1998-2013	40	Minimum 24	70	

Abbreviations: CO₂ TOLMS, transoral CO₂ laser microsurgery; LC, local control; LP, larynx preservation.

Table 3. Oncological Outcomes of Patient Treated With OPL.

Author (year)	Treatment period	Patients	Follow-up (months)	LC 5 years (%)	LP 5 years
Succo (2016) ⁶⁵	1995-2011	207	63	97.5%	98%
Giovanni (2001) ⁶⁶	1982-1997	65		92%	92%
Camprette (1998) ⁶⁷	1984-1993	23	Minimum 15	83%	
Spector (1999) ⁶⁸	1971-1989	71	Minimum 60s	93%	93%

Abbreviations: LC, local control; LP, laryngeal preservation; OPL, open partial laryngectomy.

Table 4. Weighted Averages of the Oncological Outcomes for CO₂ TOLMS, RT, or OPL.

Treatment	Patients	LC 5 years (%)	Patients	LP 5 years (%)
CO ₂ TOLMS	1362	75.4	1094	87
RT	3365	75.63	346	82.4
OPL	366	94.40	343	95.8

Abbreviations: CO₂ TOLMS, transoral CO₂ laser microsurgery; LC, local control; LP, larynx preservation; OPL, open partial laryngectomy; RT, radiotherapy.

evidence regarding the effectiveness of one treatment over the other.¹⁻⁴ The results of the current review show that weighted averages for LC and LP is higher with OPL (94.4% and 95.8%) compared to CO₂ TOLMS (75.4% and 87%) and RT (75.6% and 82.4).

Our systematic review shows that the number of patients treated with OPL was lower than that of patients treated with CO₂ TOLMS and RT; this suggests that the role of open surgery for management of laryngeal cancer has gradually decreased during the past 20 years probably because of the worse functional outcomes as voice quality and swallowing results. The development of CO₂ TOLMS and improvements

in delivery of RT have replaced the previously standard techniques of OPL for early cancer. In the recent years, CO₂ TOLMS has received a great consensus, as the use of CO₂ TOLMS as a primary treatment is more cost-effective than OPL or RT,⁶⁹⁻⁷¹ and it is usually performed as a day case procedure. Moreover, a number of optical and molecular examining technologies have been developed over the last few years to improve tumor detection and tumor margin identification. One of the most implemented techniques in clinical practice is narrow-band imaging (NBI); a significant reduction of positive superficial margins was found in patients treated with intraoperative use of NBI (52%) compared to patients treated without intraoperative NBI (28.6%; $P < .05$).⁷²

Laryngeal Preservation

The CO₂ transoral laser microsurgery resulted in higher LP compared to RT; this can be explained by the preservation of physiological cartilage barriers. Furthermore, laser surgery can be repeated or followed by other treatment protocols (eg, RT or OPL) in patients with recurrent disease. Contrarily, both RT and OPL in primary glottic carcinoma may lead to treatment limitations in case of recurrence, making organ preservation

more unlikely. In addition, patients undergoing salvage surgery post-RT have a greater number of complications than patients post-CO₂ TOLMS. Overall complication rate in salvage surgery post-RT ranges from 5% to 78% with the most common complication being pharyngocutaneous fistula formation occurring in as many as 73% of cases in the salvage setting.^{73,74}

Local Control

Evidence confirms that patients with T2b and vocal cord mobility have a poorer prognosis and LC compared to patients with T2a tumors for both CO₂ TOLMS^{3,55} and RT^{9,10,13,27,28,30,75,76} while data on OPL are not enough to evaluate the oncological outcomes in these patients. In a recent case series, Succo et al⁶⁵ affirmed that OPL is safer in case of T2b compared to CO₂ TOLMS; however, it led to more dysfunctional sequelae. The authors concluded that OPL should be performed in selected patients affected by glottic cT2 with impaired mobility of vocal cords and suspected extension to the paraglottic space (PGS). Rucci et al⁷⁷ observed that the dorsal compartment of the glottic site is in close proximity to the paraglottic space. The internal cricoarytenoid ligaments oppose for a short length of time to the penetration of early glottic cancer into the paraglottic space toward the cricoarytenoid joints. Lesions invading the paraglottic space should be correctly classified as T3 during the preoperative evaluation with a transnasal flexible videofiberscope and magnetic resonance imaging.⁷⁸ Poorer prognosis seems to be associated mainly with tumor infiltration of the posterior paraglottic space resulting in fixation of the arytenoid joint and not with impaired mobility from vocal fold muscle infiltration or pure tumor bulk.⁶

Involvement of the Anterior Commissure

The treatment of the T2 glottic cancer with involvement of anterior commissure (AC) is also controversial. Laccourreye et al⁷⁹ found that among 416 patients with T1 or T2 laryngeal cancers undergoing vertical partial laryngectomies, the failure rate was 23% if the AC was involved; higher than at other anatomic subsites. Studies on CO₂ TOLMS^{52-54,58,59,63} and studies on RT^{20,21,24,25,76} analyzed the involvement of the AC and concluded that its involvement did not result in a significantly lower overall survival rate. However, Hoffmann et al (96 patients) and Carta et al (105 patients), in large sample-sized studies, revealed a significantly increased risk for local recurrences in patients with extensive infiltration of the AC.^{59,63,80}

The vertical plane of the AC has been identified as a laryngeal subsite at risk for local treatment failures.⁸¹⁻⁸⁴ In the ventral compartment, cancer can easily diffuse superficially along the ventral mucosa containing blood vessels and glands; this diffusion usually follows a cranial-to-caudal direction. Moreover, if cancer reaches in depth the Broyles tendon, it can invade adjacent structures. Therefore, an early-stage carcinoma with involvement of the AC could penetrate the cartilage transforming a T1 tumor into a T4 switch, thus representing a

contraindication for CO₂ TOLMS. The impact of the AC involvement on prognosis in laryngeal cancer remains a topic with inconsistent results in the literature; a detailed stratification of tumors involving the AC needs to be investigated in further studies for all treatment modalities.⁸⁵

Limits of the Study

The main limitation of this review is the vast heterogeneity of selected studies. Radiotherapy studies have a large variety in technique, fraction size, and overall dose, while CO₂ TOLMS studies did not describe which resections were performed during surgery. Furthermore, there are no randomized trials or comparison studies; all the selected studies are retrospective case series. For this reason, formal statistical analysis and meta-analysis are inappropriate. It is very important to underline that in the majority of studies on CO₂ TOLMS, there was some selection of patients. Large T2 tumor or tumor with the involvement of AC may not be suitable for a transoral approach, and treatment must be individualized according to patient anatomy. Finally, there was heterogeneity in treatment details, treatment period, study design, and follow-up for both treatment modalities.

Conclusions

The current first-line treatments for early laryngeal cancer are CO₂ TOLMS and RT, while the role of OPL has greatly diminished in the last 20 years. This review suggests that CO₂ TOLMS should be encouraged in selected T2 patients, because LC is comparable but primary treatment with CO₂ TOLMS results in higher LP compared to primary treatment with RT. In conclusion, data suggest that involvement of the AC in the craniocaudal plane and T2b impaired vocal cord mobility have a poorer prognosis and LC compared to patients with T2a tumors for both CO₂ TOLMS and RT. Open partial laryngectomy should be proposed in selected patients affected by glottic cT2 with impaired mobility of vocal cords and suspected extension to the PGS. Further studies on cancers with the involvement of AC and impaired vocal cord are necessary to clarify their impact on oncological outcomes, and prospective randomized controlled studies for both treatment modality are required to confirm these results.

Authors' Note

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.


Declaration of Conflicting Interests


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ORCID iD

Massimo Ralli  <https://orcid.org/0000-0001-8776-0421>

Francesca Yoshie Russo  <https://orcid.org/0000-0001-5244-2423>

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